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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/192,064	11/13/1998	HARTOUN HARTOUNIAN	07333/043001	9320

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT PAPER NUMBER

1615

DATE MAILED: 06/21/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/192,064

Applicant(s)
Hartounian

Examiner
Gollamudi Kishore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Apr 8, 2002
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 12-47, and 49-53 is/are pending in the application.
- 4a) Of the above, claim(s) 36-47 and 50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10, 12-35, 49, and 51-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:

- ☐ Certified copies of the priority documents have been received.
- ☐ Certified copies of the priority documents have been received in Application No. _____.
- ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
- ☐ Interview Summary (PTO-413) Paper No(s). _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other:

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DETAILED ACTION

The request for the extension of time and response dated 4-8-02 are acknowledged.

Claims included in the prosecution are 1-10, 12-35, 49 and 51-53.

Claims 36-47 and 50 remain withdrawn from consideration.

Claim Rejections - 35 U.S.C. § 103

- 1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:**

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

- 2. Claims 1-10, 12-35, 49 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol., 1994) or Kim (5,723,147) or Sankaram (5,766,627) in view of Lenk (5,48,441).**

The above references of Kim, 1987, Assil, 1987, Bonetti 1994 or Kim 147 or Sankaram, 627 all teach basically the same process of preparation of multivesicular liposomes.

The process involves dissolving the amphipathic lipid and the neutral lipid in chloroform and mixing it with an aqueous solution containing sucrose and forming an

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emulsion (instant step A), mixing this emulsion with an aqueous solution (step b) and removing the organic solvent and thereby forming the multivesicular liposomes (note the experimental sections in the publications and examples in Kim 147 and Sankaram 627).

What is lacking in these references is the teachings of filtration by cross-flow filtration method and making a sterile preparation.

Lenk while disclosing a method for size separation of particles teaches that there are problems associated with various methods previously available for the preparation of liposomes or vesicles of a select size and that by the cross-filtration method (also called as tangential flow filtration method) allows one to select large quantities of liposomes of a homogeneous, defined size distribution from a heterogeneously-sized population (note the abstract, col. 4, line 12 through col. 6, line 49). Lenk also discloses preparations for various modes of administration and sterile solutions (note col. 15, lines 1-19 and examples).

The use of cross-flow filtration step in the method of preparation of multivesicular lipid particles of Kim, Assil, Bonetti or Sankaram would have been obvious to one of ordinary skill in the art since Lenk teaches the advantages of using such a step in the preparation of vesicles or liposomes. It is deemed within the skill of the highly developed sciences to prepare a sterile preparation. It is also within the skill of the art to realize that if any composition is given by a systemic route, in the form of an injection in particular, that the preparation should be sterilized. Furthermore, it is clearly evident from Lenk that sterile preparations have to be used if they are administered to mammals. The criticality of

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the type of mixers and various method parameters recited in instant claims is not readily apparent to the examiner. In the absence of unexpected and unobvious results, these are deemed to be parameters manipulated by an artisan to obtain the best possible results. It is common practice in any field to perform a pilot method and extend it to a large scale production.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments are based on only Lenk's reference which teaches cross-flow filtration and not regarding the primary references which teach the claimed process itself, but lacking in sterilizing. A careful review of the prosecution history of the application indicates that applicant introduced the limitation of 'cross-flow filtration' in the independent claim 1 through amendment dated 1-16-01 and argued the lack of teachings of the cross-flow filtration in the methods taught in the primary references of Kim, Assil, Bonetti and Sankaram and the superior results obtained by the inclusion of the step of cross-flow filtration in instant invention. The examiner then included Lenk which teaches the advantages of using cross-flow filtration. Now it would appear from applicant's arguments that this cross-flow filtration step is not critical at all and that cross-flow filtration is not used as a method of controlling the size distribution of the particles produced according to the inventive method. These arguments appear to be contradictory to applicant's earlier arguments dated 1-16-01. As already set forth in the rejections, the primary references teach the same method and the references lack only the sterilization

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step and the cross-flow filtration step. Therefore, one can reasonably come to the conclusion that same results are obtained in prior art as in instant invention (since the methods are the same and cross-filtration is not critical). The examiner also points out that the motivation to use cross-flow filtration need not be the same as applicant's.

3. Claims 1-10, 12-35, 49 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (cancer Treatment Reports, 1987) or Assil (arch. Ophthalmol. 1987) or Bonetti (Cancer Chemother. Pharmacol., 1994) or Kim (5,723,147) or Sankaram (5,766,627) in view of Lenk as set forth above, further in view of Kwasiborski (6,033,708), Fenski (5,837,282), Mehl (5,885,260), Castor (5,776,486), Moynihan (5,589,189) by themselves or in combination.

Kwasiborski (708) and Fenski (282) both teach a method of preparation of sterile liposome dispersion; the method involves filtering through 0.2 micron filters (note the examples and claims of Kwasiborski; col. 11, line 40 et seq.).

Mehl (260) while disclosing sterile liposome preparations teaches that administration to humans requires that the liposomes be pyrogen free and sterile and advocates the use of filters (note col. 3, line 54 et seq.).

Castor teaches the awareness in the art of sterilizing individual components and solutions and the filtration of liposomes (note col. 2, line 37 et seq.).

Moynihan teaches that the best method for terminal sterile filtration is the sequential filtration of a dispersed liposomes (note col. 3, line 33 et seq.).

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One of ordinary skill in the art would be motivated to prepare the multivesicular liposomes in a sterile state because the references of Kwasiborski, Fenski, Mehl, Castor and Moynihan each teach methods that involve the production of sterile liposomes and therefore, a similar sterile production of liposomes is to be expected with instant liposomes also.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that these references do not teach cross-flow filtration. The examiner agrees and points out that these references are combined to show that sterilization is commonly practiced in the art of liposomes; as already pointed out above, Lenk teaches this filtration method and advantages of using this method.

4. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

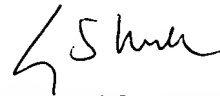
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.



Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

June 20, 2002